**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| In re Application of: | : | |
| | : | |
| Jérôme Asius et al. | : | |
| | : | |
| Serial No.: 09/242,103 | : | Art Unit: 3738 |
| | : | |
| Filed: February 8, 1999 | : | Examiner: C. Koh |
| | : | |
| For: IMPLANT FOR SUBCUTANEOUS OR INTRADERMAL INJECTION | : | Atty Docket: 20198/0047 |

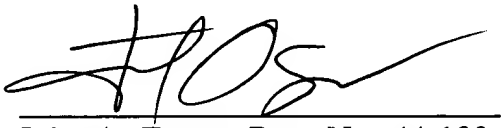
**SUBMISSION OF VERIFICATION OF TRANSLATION**

Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned attorney respectfully submits in the above-captioned application the Verification of Translation for French Patent Application No. 97 07334 filed in the name of Biopharmex Holding SA.

Respectfully submitted,



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Telephone: 202-331-7111

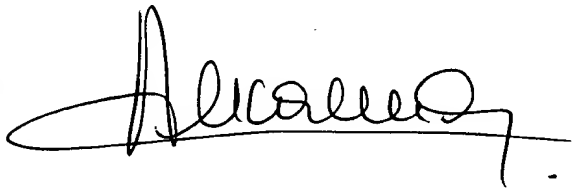
Date: February 1, 2002

IN THE MATTER OF FRENCH PATENT APPLICATION N° 97 07334 FILED ON
IN THE NAME OF BIOPHARMEX HOLDING SA



## VERIFICATION OF TRANSLATION

I, Laurence VERCAEMER, CABINET PLASSERAUD, 84 rue d'Amsterdam, 75440 PARIS CEDEX 09 hereby certify that the following is a true translation to the best of my knowledge and belief of the priority document.

Signature 

Paris, January 11, 2002

FRENCH REPUBLIC

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# PATENT

## UTILITY CERTIFICATE – CERTIFICATE OF ADDITION

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The Director of the National Institute of Industrial Property certificates that the attached document is a true copy of an application for industrial property titleright filed at the Institute.

**Drawn up in Paris, October 27, 1997**

**On behalf of the Director of the National Institute of Industrial Property**
**The Divisional Head**

**(signature)**

**Martine PLANCHE**

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PATENT

Cerfa N° 11354*01

# UTILITY CERTIFICATE

Intellectual Property Code - Book VI

## REQUEST FOR GRANT 1 / 2

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| SUBMISSION OF THE DOCUMENTS DATE | June 13, 1997 |
| PLACE | |
| NATIONAL REGISTRATION N° ALLOTTED BY THE NIIPI | 97 07334 |
| FILING DATE ALLOTED BY THE NIIP | June 13, 97 |

**1 NAME AND ADRESS OF THE APPLICANT OR THE REPRESENTATIVE TO WHOM THE CORRESPONDANCE IS TO BE ADDRESSED**

**Maître Marie-José LEFEBVRE**
**Avocat à la Cour**
**104 av. Victor Hugo 75016 PARIS**



**Your references for this file :** *(optional)*

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| Divisional application<br>*Initial patent application*<br>*or Initial certificate of utility application* | ☐<br>N° Date<br>N° Date |
| Conversion of a European patent Application<br>*Initial patent application* | ☐<br>N° Date |

**3 TITLE OF THE INVENTION** (maximum 200 characters)
**Injectable implant for subcutaneous or intradermal injection, with a controlled resorbability, for reparative or plastic surgery and esthetic dermatology**

| | |
|---|---|
| **4 PRIORITY DECLARATION OR APPLICATION FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION** | Country or organisation<br>Date / / N°<br>Country or organisation<br>Date / / N°<br>Country or organisation<br>Date / / N°<br>☐ **If there are additional priorities, check the box and use the additional form « suite »** |
| **5 APPLICANT** | ☐ **If there are additional applicants, check the box and use the additional form « Suite »** |
| Name or Company name | BIOPHARMEX HOLDING SA |
| First name(s) | |
| Legal form | SA |
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| APE-NAF Code | |
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# UTILITY CERTIFICATE

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| **Your references for this file** *(optional)* | | | |
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| **7 INVENTOR (S)** | | | |
| The Inventors are the applicants | | ☐ Yes<br>☒ No **In this case provide a separate designation of inventor(s)** | |
| **8 SEARCH REPORT** | | **Only for a patent application (including division and transformation)** | |
| Request for immediate examination | | ☒ | |
| Or deferred examination | | ☐ | |
| Payment at intervals of the fee | | **Payment in two stages, only for individuals** | |
| | | ☐ Yes | |
| | | ☐ No | |
| **9 REDUCTION OF FEES** | | **Only for individuals**<br>☐ Requested for the first time *(Attach copy of the income-tax form)*<br>☐ Requested prior to filing *(Attach copy of the favourable decision or indicate its reference) :* | |
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# PATENT

Cerfa
N° 11235*02

## UTILITY CERTIFICATE
Intellectual Property Code – Book VI

## DESIGNATION OF INVENTOR(S) Page No. 1/2
**(if the Applicant is not the Inventor or the sole Inventor)**

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| | |
|---|---|
| **Your references for this file** *(optional)* | |
| **NATIONAL REGISTRATION N°** | 97 07334 |

**TITLE OF THE INVENTION** (maximum 200 characters)

Injectable implant for subcutaneous or intradermal injection, with a controlled resorbability, for reparative or plastic surgery and esthetic dermatology

**APPLICANT(s)**

BIOPHARMEX HOLDING SA
11 Boulevard Royal
L-2449 Luxembourg

**DESIGNATE(S) AS INVENTOR(S) :** (If there are more than 3 inventors, use an additional identical form and number each page, indicating the total number of pages)

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N° 11235*02

# UTILITY CERTIFICATE

Intellectual Property Code – Book VI

## DESIGNATION OF INVENTOR(S) Page No. 2/2

**(If the Applicant is not the Inventor or the sole Inventor)**

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| Address | Street | | |
| | Postal code and City | | |
| Company name *(optional)* | | | |

**10 SIGNATURE OF THE APPLICANT OR REPRESENTATIVE**
(Name and capacity of the signatory)

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# DOCUMENT COMPRISING AMENDMENTS

| Page(s) of the description or claims or drawing sheet | | | R.M.* | Date of letter | Date stamp of examiner |
|---|---|---|---|---|---|
| Amended | Deleted | Added | | | |
| 1, 3, 4, 5 | - | - | RM | Aug. 14, 97 | Sept. 8, 97 / J.A.B. |

An amendment in the original claims, unless resulting from the disposition of article 28 of the Decret of Sept. 19, 1979, is signaled by the mention "RM" (Revendications Modifiées = amended claims).

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An amendment in the original claims, unless resulting from the disposition of article 28 of the Decret of Sept. 19, 1979, is signaled by the mention "RM" (Revendications Modifiées = amended claims).

The present invention relates to an implant for subcutaneous or intradermal injection, resorbable in a given time, intended to be used in reparative or plastic surgery and in esthetic dermatology, for filling wrinkles, fine lines, skin cracks, acne scars and other scars. The characteristics of the product are the ease of use without prior manipulations, the syringebility of the product, the efficacy of the microspheres which favor fibrosis, the resorbability in a controlled period of time of the microspheres as well as of the vector gel, the absence of allergenicity of the product, which makes any prior test unnecessary.

Up until now, a number of products have been used. Each product has advantages and disadvantages :

- Silicone gel (or silicone oil) is easy to use. However, the migration of droplets of silicone into the tissues situated below the point of injection, by simple gravity, has been observed after injection. Silicone is frequently the cause of chronic inflammation, of formation of granulomas, and even of tardive allergic reactions. Silicone is not biodegradable, and it is often found in the liver.

- Teflon paste is a suspension of polytetrafluoroethylene particles (diameter 10 to 100 $\mu$m) in glycerine. This product, in numerous cases, caused severe and chronic serious infections and had to be removed after a few months from dermal and subdermal tissues for most patients. It has also been proved that small polytetrafluoroethylene particles were found in the liver.

- Collagen suspensions have been very widely used in the last ten years. The results have however been quite disappointing since collagen is resorbed within 1 to 3 months. Allergic reactions are also noted in about 2% of patients . Finally, it should be noted that collagen is of bovine origin.

- Biological samples from the patient herself/himself: the idea was certainly interesting, but clinical experience has shown the failure of the reimplantation of the fatty cells, which are absorbed and disappear within a few weeks.

Another system consisted in adding plasma from the patient to a collagen gelatin of bovine and porcine origins. The results are even more disappointing, and the product is of animal origin.

- Hyaluronate gels provided a good alternative by virtue of their biocompatibility and their lack of toxicity. They are moreover widely used in eye surgery. However, their rapid bioresorbability (maximum 2 months) makes them ineffective for use in plastic surgery.

- Bioplastics are polymerized silicone particles (diameter 70 to 140 $\mu$) dispersed in polyvinylpyrrolidone. The product had to be withdrawn given the chronic inflammation and the rejection reactions caused by it.

D

- Polymethylmethacrylate (PMMA) microspheres having a diameter of 20 to 40 μ in suspension either in a solution of gelatin or in a solution of collagen. PMMA is not biodegradable, but not enough time has elapsed in order to know what this implant gives after 5 or 6 years. Moreover, the vector remains a solution of collagen of bovine origin, with the problems of allergy which are known for it.

The product of the invention is an implant :

- resorbable in a controlled manner. The idea is first to have an implant which is resorbable after 1 year, to allow for possible esthetics corrections. Secondly, the implant will only be resorbed after 3 years. In no case does a non-resorbable implant appear to be desirable. It is still a foreign body placed in a live tissue.

- based on the principle of microspheres in suspension in a gel. These microspheres should have a diameter higher than 5 $\mu$, and preferably higher than 20 $\mu$, so as not be absorbed by macrophages. They should have a diameter lower than 150 $\mu$, and preferably lower than 40 $\mu$, so as on the one hand to be injectable by a fine needle and on the other hand not to create granular masses under the finger.

- these microspheres are constituted of a neutral polymer chosen for its innocuousness and already largely used by the pharmaceutical industry either orally or parenterally.

The microspheres should have a controlled bioresorbability, to be adapted to the two types of product described here above, either in a first aim with a resorbability period of up to 1 year or, in a second aim, with a resorbability period of 1 to 3 years. This means that the polymer will degrade itself in situ into compounds of low molecular weight which will be eliminated from the organism by natural processes.

Two families of polymers essentially meet the preceding definition : the polycaprolactones (and in particular the poly-ε-caprolactones), the lactides (polylactic acids or PLA) and glycosides (polyglycolic acids or PLAGA).

Given the numerous studies already carried out and the good knowledge of the products, in particular as regards the manufacture of microspheres and resorbability, it appears advantageous to use a mixture of polylactic acid (PLA) and polylactic-co-glycolic acid (PLAGA). The proportions of each of these two acids make it possible to determine the remanence of the product.

Bioresorbable synthetic polymers have been studied for about 15 years under the direction of Michel VERT, Director of Research at C.N.R.S. The first clinical uses of PLAs started in 1981 for various indications in facial traumatology. The use of lactic acid polymers has become systematic in the context of bioresorbable surgical implants. PLAs now have

diverse and wide medical applications (bone surgery, maxillo-facial surgery, controlled-release pharmacological formulations: implants, microspheres, nanospheres, vaccines).

The degradation of lactic acid polymers in biological medium occurs exclusively by a chemical mechanism of nonspecific hydrolysis. The products of this hydrolysis are then metabolized and then eliminated by the human body. Chemical hydrolysis of the polymer is complete; the more pronounced its amorphous character and the lower its molecular mass, the more rapidly it occurs. The biocompatibility of the PLA and PLAGA polymers makes them excellent supports for cellular growth and tissue regeneration.

The microspheres are included in a gel. This gel, which is used as vector to maintain the microspheres in a homogeneous suspension, is resorbable within approximately 2 months, which corresponds to the time necessary for the creation of fibroses around the microspheres. It consists mainly of water for injection and a gelling agent authorized in injection: cellulose derivatives, and more particularly carboxymethylcellulose (CMC) at a concentration of 0.1 to 7.5%, and preferably from 0.1 to 5.0%. It is also possible to use hydroxypropylmethylcellulose (HPMC) which is commonly used in intra-ocular injection in the context of cataract operations. It is also possible to use a synthetic hyaluronic acid, which is used for intra-ocular injections and subcutaneous injections. It is also possible to use lactic acid esters, caproic acid esters and the like.

The good dispersion of the microspheres and the homogeneity of the gel will be provided by the use of a surfactant chosen for its innocuousness and its authorized subcutaneous and intradermal use. Tween 80 or pluronic acid can be used.

- The product is provided in ready-for-use prefilled sterile syringes, provided with a needle, or in vials of sterile suspension.
- The implant does not require a test of allergenicity. It does not contain any product of animal origin.

The protocol for the manufacture of the implant is described below :

- Preparation of microspheres of lactic acid polymer. The conventional solvent evaporation technique, or the so-called controlled precipitation technique or any other technique which makes it possible to obtain microspheres of the desired size is used.
- Preparation of a gel of sufficient viscosity to maintain the microspheres in suspension. This viscosity will be adjusted depending on the size of the microspheres and the proportion of microspheres dispersed in the gel. This proportion will be from 5 to 30 % (weight/volume) preferably from 10 to 20 %.
- Distribution of the gel into syringes or into vials, in a controlled atmosphere (class $10^4$).

- Sterilization of the vials or syringes, or use of a process which makes the finished product suitable for injection by the subcutaneous route.

Examples of finished products according to the invention :

**EXAMPLE A**

2 g of PLA are dissolved in 20 ml of an organic solvent (ethylacetate). This solution is dispersed in 100 ml of water containing 5 g of surfactant (Tween 80). Moderate vortex stirring is maintained until evaporation of the solvent and formation of microspheres having a mean diameter of 40 µ. The microspheres formed are recovered by sedimentation, filtration and drying. They are then included in a gel consisting of water and CMC (0.5%) . After moderate stirring, the distribution is carried out.

**EXAMPLE B**

2 g of PLA are dissolved in 20 ml of an organic solvent (methylene chloride). This solution is dispersed in 100 ml of water containing 5 g of surfactant (Tween 80). Moderate vortex stirring is maintained until evaporation of the solvent and formation of microspheres having a mean diameter of 80 µ. The microspheres formed are recovered by sedimentation, filtration and drying. They are then included in a gel consisting of water and CMC (0.5%). After moderate stirring, the distribution is carried out.

**EXAMPLE C**

2 g of PLA are dissolved in 20 ml of an organic solvent (chloroform). This solution is dispersed in 100 ml of water containing 5 g of surfactant (Tween 80). Moderate vortex stirring is maintained until evaporation of the solvent and formation of microspheres having a mean diameter of 50 µ. The microspheres formed are recovered by sedimentation, filtration and drying. They are then included in a gel consisting of water and HPMC (1%). After moderate stirring, the distribution is carried out.

## Claims

1. Injectable implants consisting of bioresorbable microspheres in suspension in a gel.

2. Implants according to Claim 1, characterized in that the microspheres consist of poly-ε-caprolactone, lactic acid polymers, lactic co-glycolic acid polymers, lactides, glycosides, or a mixture thereof.

3. Implants according to Claim 1 , characterized in that the proportion of microspheres in the gel is from 5 to 30 %, preferably from 10 to 20 %.

4. Implants according to Claim 1, characterized in that the microspheres have a mean diameter of from 5 to 150 μ, and preferably from 20 to 40 μ.

5. Implants according to Claim 1, characterized in that the microspheres are bioresorbable within a period of 6 months to 3 years.

6. Implants according to Claim 1, characterized in that the gel medium includes mainly, as gelling agent, carboxymethylcellulose (CMC) at a concentration of 0.1 to 7.5%, and preferably from 0.1 to 5.0%.

The present invention relates to an implant for subcutaneous injection, resorbable in a given time, intended to be used in reparative or plastic surgery and in esthetic dermatology, for filling wrinkles, fine lines, skin cracks, acne scars and other scars. The characteristics of the product are the ease of use without prior manipulations, the syringebility of the product, the efficacy of the microspheres which favors fibrosis, the resorbability in a controlled period of time of the microspheres as well as of the vector gel, the absence of allergenicity of the product, which makes any prior test unnecessary.

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- Bioplastics are polymerized silicone particles (diameter 70 to 140 $\mu$) dispersed in polyvinylpyrrolidone. The product had to be withdrawn given the chronic inflammation and the rejection reactions caused by it.

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- Preparation of a gel of sufficient viscosity to maintain the microspheres in suspension. This viscosity will be adjusted depending on the size of the microspheres and the proportion of microspheres dispersed in the gel. This proportion will be from 5 to 30 % (weight/volume) preferably from 10 to 20 %.
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1. Injectable implants consisting of bioresorbable microspheres in suspension in a gel.

2. Implants according to Claim 1, characterized in that the microspheres consist of poly-ε-caprolactone, lactic acid polymers, lactic co-glycolic acid polymers, lactides, glycosides, or a mixture thereof.

3. Implants according to Claim 1 , characterized in that the proportion of microspheres in the gel is from 5 to 30 %, preferably from 10 to 20 %.

4. Implants according to Claim 1, characterized in that the microspheres have a mean diameter of from 5 to 150 μ, and preferably from 20 to 40 μ.

5. Implants according to Claim 1, characterized in that the microspheres are bioresorbable within a period of 1 year to 3 years.

6. Implants according to Claim 1, characterized in that the gel medium includes mainly, as gelling agent, carboxymethylcellulose (CMC) at a concentration of 0.1 to 7.5%, and preferably from 0.1 to 5.0%.